The modality dependent target margins to cover 95% of the tumor outer contour were 5.6 mm, 8.7 mm and 6.2 mm and resulted in median target volumes of 56 ml, 72 ml and 53 ml for CT, MRI and PET, respectively (Fig. 1b).

**Conclusion:** In all modalities, delineated GTVs overestimated tumor volume. Nevertheless, some tumor volume was missed in all cases. Automated delineation on PET resulted in the smallest target volume compared to manual delineation on CT and MRI, while covering an equivalent amount of tumor. This study suggests that delineation or segmentation inaccuracies can be corrected using a margin between 5.6 and 8.7 mm.

**PV-0516**

**Guideline development for tumor delineation on MR-images for laryngeal and hypophargeal cancer**

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**Purpose or Objective:** Development of guidelines for the delineation of the gross tumor volume (GTV) on MRI is of utmost importance to benefit from the increased visibility of anatomical details and to achieve a more accurate and precise GTV delineation. In the ideal situation, the GTV corresponds to the histopathologically determined "true tumor volume". In this work we developed and validated guidelines for GTV delineation on MRI by comparison with the tumor outline on histopathology as gold standard.

**Material and Methods:** Twenty-seven patients with T3 or T4 laryngeal or hypopharyngeal cancer underwent a MRI scan before total laryngectomy. After surgery, whole-mount hematoxylin-eosin stained (H&E) sections were obtained from the surgical specimen. One pathologist delineated all tumor tissue on the H&E sections (tumorH&E). The GTV was delineated on the MR images (T1 w, Gd-T1 w, T2 w) by three independent observers in two sessions. The first session (delineation 1) was performed according to clinical practice. In the second session (delineation 2) the observers used delineation guidelines derived from guidelines for detection of cartilage invasion on MRI: Volumes with increased signal intensity on T2w images and higher signal intensity on Gd-T1w images than that of the tumor bulk were not included in the GTV.
The reconstructed specimen was registered to the MR images in order to compare the GTV to the tumorH&E in 3D. Volumes and overlap parameters were analyzed. Distances between the GTV and the tumorH&E were calculated at locations where the tumorH&E was outside the GTV. Subsequently, a margin that accounted for the underestimation of the tumour was determined. Finally, target volumes were created by applying this margin to the GTV.

**Results:** The median GTVs of delineation 1 (19.4 cm3) and of delineation 2 (15.8 cm3) were larger than the volume of the tumorH&E (10.5 cm3). However, target margins of 10.2 mm and 8.3 mm were needed for delineation 1 and 2 , respectively, to compensate for the underestimation of the tumor at specific locations. By adding this margin to the GTVs, the target volumes for delineation 1 (median: 117.6 cm3, mean: 125.9 cm3, SD: 53.2 cm3) were significantly larger than those for delineation 2 (median 76.2 cm3, mean 85.7 cm3, SD: 43.3 cm3).

**Conclusion:** GTV delineation guidelines on MRI decreased the overestimation of the tumour, resulted in a smaller margin around the delineated GTV needed to include all tumor tissue and consequently resulted in smaller target volumes with the same tumor coverage.

**PV-0517**

**Upfront vs. no upfront neck dissection in primary head and neck cancer radio(chemo)therapy**

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**Purpose or Objective:** The benefit of upfront neck dissection (ND) in locally advanced head and neck cancer (HNC) treated with primary (chemo-) radiotherapy (CRT) is debated. Therefore, we retrospectively compared outcome and toxicity between patients with and without upfront ND followed by CRT.

**Material and Methods:** Two-hundred sixty-four consecutive patients with HNC without metastases at diagnosis and with lymph node stage N2-N3 were included in 2 centers. Patients were all treated between January 2002 and December 2012, and received definitive CRT in center 1 and upfront ND followed by CRT in center 2. Clinical data and outcome were assessed retrospectively. Toxicity was scored using the LENT-SOMA scale at 6, 12, 18 and 24 months after the end of treatment.Both patient groups were compared using a Chi-square test for categorical variables or a Mann-Whitney U test for continuous variables. Descriptive statistics on overall survival (OS) is based on Kaplan Meier estimates. For all other time-to-event outcomes, cumulative incidence function (CIF) estimates were calculated. The difference between both groups on the different outcomes was analyzed using multivariable models, including group and prognostic patient- or tumor characteristics on which the 2 groups were different. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

**Results:** We included 150 patients in the group without ND (center 1) and 114 patients in the group with upfront ND (center 2). The group comparison is given in *Table 1*.

| Variable | Statistic | No dissection | Neck dissection | P-value |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | n/N (%) | 126/150 ( 84.00%) | 103/114 ( 90.35%) | 0.132 |
| Female | n/N (%) | 24/150 ( 16.00%) | 11/114 ( 9.65%) | |
| **Diagnosis age** | N | 150 | 114 | 0.794 |
| | Mean | 58.9 | 59.0 | |
| | Std | 8.78 | 8.67 | |
| | Median | 58.0 | 58.9 | |
| | IQR | (52.0; 65.0) | (52.4; 65.4) | |
| | Range | (38.0; 81.0) | (40.1; 86.8) | |
| **T stage** | | | | |
| 0 | n/N (%) | 0/150 ( 0.00%) | 1/114 ( 0.88%) | 0.001 |
| 1 | n/N (%) | 7/150 ( 4.67%) | 12/114 ( 10.53%) | |
| 2 | n/N (%) | 36/150 ( 24.00%) | 39/114 ( 34.21%) | |
| 3 | n/N (%) | 39/150 ( 26.00%) | 37/114 ( 32.46%) | |
| 4 | n/N (%) | 68/150 ( 45.33%) | 25/114 ( 21.93%) | |
| **N stage** | | | | |
| 2A | n/N (%) | 8/150 ( 5.33%) | 6/114 ( 5.26%) | 0.182 |
| 2B | n/N (%) | 63/150 ( 42.00%) | 59/114 ( 51.75%) | |
| 2C | n/N (%) | 73/150 ( 48.67%) | 41/114 ( 35.96%) | |
| 3 | n/N (%) | 6/150 ( 4.00%) | 8/114 ( 7.02%) | |
| **Subsite** | | | | |
| Oral cavitity | n/N (%) | 13/150 ( 8.67%) | 6/114 ( 5.26%) | 0.526 |
| Orofarynx | n/N (%) | 66/150 ( 44.00%) | 46/114 ( 40.35%) | |
| Hypofarynx | n/N (%) | 53/150 ( 35.33%) | 49/114 ( 42.98%) | |
| Larynx | n/N (%) | 18/150 ( 12.00%) | 13/114 ( 11.40%) | |
| **IMRT** | | | | |
| No | n/N (%) | 64/150 ( 42.67%) | 42/114 ( 36.84%) | 0.339 |
| Yes | n/N (%) | 86/150 ( 57.33%) | 72/114 ( 63.16%) | |
| **Overall treatment time radiotherapy** | N | 150 | 114 | <.001 |
| | Mean | 43.4 | 44.9 | |
| | Std | 3.29 | 2.73 | |
| | Median | 43.0 | 44.0 | |
| | Interquartile range | (41.0; 44.0) | (43.0; 46.0) | |
| | Range | (37.0; 58.0) | (39.0; 61.0) | |
| **Concomitant treatment** | | | | |
| No | n/N (%) | 22/150 ( 14.67%) | 26/114 ( 22.81%) | 0.089 |
| Yes | n/N (%) | 128/150 ( 85.33%) | 88/114 ( 77.19%) | |
| **Type concomitant treatment** | | | | |
| Cisplatinum | n/N (%) | 109/128 ( 85.16%) | 83/87 ( 95.40%) | 0.017 |
| Cetuximab | n/N (%) | 19/128 ( 14.84%) | 4/87 ( 4.60%) | |
| **HPV status Oropharynx** | | | | |
| Positive | n/N (%) | 13/66 (19.70%) | 10/46 (21.74%) | 0.752 |
| Negative | n/N (%) | 44/66 (66.67%) | 31/46 (67.40%) | |
| Unknown | n/N (%) | 9/66 (13.64%) | 5/46 (10.87%) | |

*Table 1.* Group comparison on patient/tumor characteristics.

Based on this result, we decided to account for the differences in T stage, overall treatment time and concomitant treatment for the statistical analysis of outcome and toxicity. Mean follow up was 5.68 years in the group without ND and 5.83 years in the group with upfront ND. Local, regional and distant control after 2 years were 91.07% and 85.96% ($p$ = 0.09), 89.22% and 83.27% ($p$ = 0.12) and 76.74% and 75.13% ($p$ 0.92) in the group with and without upfront ND, respectively . We observed worse OS after 2 years in the subgroup with upfront ND (48.01% vs. 70.79%, $p$ = 0.01). The difference in OS can be explained by more secondary primaries in this subgroup with upfront ND and more non-disease related deaths. We did not find a significant difference between both groups regarding edema and atrophy at 6, 12, 18 and 24 months (*Figure 1*). Regarding fibrosis, we found an overall trend towards worse outcome in the ND group at all time-points (p=0.06). A significantly higher proportion of severe fibrosis (grade ≥2) was present in the ND group (p=0.01) at all time points (*Figure 1*).

| Outcome | OR (95% CI) | P-value |
|---|---|---|
| Fibrosis | 1.558 (0.982;2.470) | 0.0595 |
| Edema | 1.251 (0.758;2.063) | 0.3810 |
| Atrophy | 1.652 (0.644;4.242) | 0.2964 |
| Severe fibrosis | 2.811 (1.384;5.710) | 0.0042 |

OR: Odds ratio, CI: Confidence interval

OR >(<) 1 means higher (lower) level on scale for Neck dissection group.

*Figure 1.* The table presents for every toxicity, the effect of group (Neck dissection versus No neck dissection) by means of odds ratios (OR) with 95% confidence intervals at all time-points (6, 12, 18 and 24 months).

**Conclusion:** Both treatment regimens have a comparable local, regional and distant control. However, fibrosis and more specifically fibrosis grade ≥2 is more prominent following upfront ND and CRT when compared to CRT alone.

**PV-0518**

**Phase 1 study of Debio 1143 in combination with Concurrent Chemo-Radiotherapy in LA-SCCHN**

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**Purpose or Objective:** Chemo-radiotherapy (CRT) plays a major role in the management of patients with locally advanced squamous cell carcinoma of head and neck (LA-SCCHN). However, loco-regional (LR) failure remains a significant problem due to the resistance to radiotherapy and chemotherapy. Inhibitors of Apoptosis Proteins (IAPs) are expressed in various cancers and are able to block caspase activation and modulate NF-kB signalling pathways. As such, they represent attractive targets to overcome resistance to both chemo- and radio-therapy. Debio 1143 is a potent orally-available IAP antagonist currently in clinical development able to radiosensitize and ameliorate the effects of platinum derivatives in multiple SCCHN models both in vitro and in vivo. A previous phase I study showed Debio 1143 as a single agent was well tolerated up to 400 mg/day q14d21. This Phase I study defined the dose limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, pharmacokinetic (PK) and pharmacodynamic (PD) of Debio 1143 in combination with CRT.

**Material and Methods:** Treatment-naïve LA-SSCHN (stage III/IV), negative HPV status for oropharynx, were treated with CRT (70 Gy in 7 weeks + cisplatin 100 mg/m2 every 3 weeks) and escalating doses of Debio 1143, administered orally once daily on days 1-14 every 3 weeks for a maximum of 3 cycles. The starting dose of Debio 1143 was 100 mg/day. Doses were escalated using a Bayesian Continuous Reassessment Method (CRM) until MTD, based on dose limiting toxicities (DLTs) observed within the first 9 weeks